UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS

ARIAD PHARMACEUTICALS, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, THE WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH, and THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE **Plaintiff,** **v.** **ELI LILLY AND CO.,** **Defendant.**	)	**Civil Action No. 02 CV 11280 RWZ** **U.S. District Judge Rya W. Zobel**

MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANT ELI LILLY'S SECOND MOTION FOR JUDGMENT AS A MATTER OF LAW

I. INTRODUCTION

Plaintiffs ARIAD Pharmaceuticals, Inc., Massachusetts Institute of Technology, The Whitehead Institute for Biomedical Research, and the President and Fellows of Harvard College submit this memorandum in opposition to Defendant Eli Lilly and Co.'s ("Lilly") second motion for judgment as a matter of law on the issues of infringement and validity. As an initial matter, Plaintiffs note that they have already submitted motions pursuant to Fed.R.Civ.P. 50(a) for judgment as a matter of law that Plaintiffs' evidence leaves no reasonable doubt but that the claims of the '516 patent are infringed by Lilly and that Plaintiffs are entitled to damages and that Lilly has failed to carry its burden of clear and convincing evidence that the claims of the '516 patent are invalid. Thus, Plaintiffs have already provided Lilly and the Court with briefs discussing how the trial

record entitles Plaintiffs to judgment as a matter of law on the issues of infringement and validity. In order to avoid burdening the Court with further papers and rehashing its contentions on infringement and validity, Plaintiffs incorporate those briefs (Docket # 320, JMOL on infringement) and (Docket # 331 for JMOL on validity) by reference as if fully set forth herein. Plaintiffs also submitted an opposition brief to Lilly's motion for summary judgment that the claims were invalid for failing to satisfy §§ 101 and 112 and incorporate that brief by reference as well. For all of the reasons stated in these briefs, Lilly's second motion for judgment as a matter of law should be denied and judgment as a matter of law granted in favor of Plaintiffs that the asserted claims 80, 95, 144 and 145 of the '516 patent are valid and infringed.

However, Lilly has also asked for judgment as a matter of law that the asserted claims are invalid under 35 U.S.C. § 101, an issue the Court had previously ruled would not be tried to the jury. Though Plaintiffs would request a hearing on the issue so that evidence specifically addressed to it may be adduced, Plaintiffs assert that based on the current record alone Lilly's motion for judgment as a matter of law of invalidity under § 101 must be denied.

II. THE ASSERTED CLAIMS RECITE PATENTABLE SUBJECT MATTER

Lilly's argument that the claims of the '516 patent are invalid under 35 U.S.C. §101 as encompassing "naturally-occurring biological processes," rests entirely upon a misreading of the claims and is unsupported by the record. The '516 claims are directed to methods which, as construed by this Court, fall squarely under the Supreme Court's long-standing definition of a process eligible for patent protection. The Supreme Court has held that a process is a "mode of treatment of certain materials to produce a given

result." *Diamond v. Diehr*, 450 U.S. 175, 183 (1981) (citing *Cochrane v. Deener*, 94 U.S. 780, 787-788 (1877)). As construed by this Court, the '516 claims require "decreasing the function of NF-kB to act as an intracellular messenger that regulates transcription of particular genes, in response to certain stimuli." Once it is understood that the claims are directed to a manipulation of the NF-κB pathway, the § 101 analysis ends.

The evidence of record further supports the import of the Court's claim construction - that the claims recite a method requiring a manipulation or intervention to reduce the effects of external influences or gene expression that induce NF-κB signaling in cells. The '516 patent claims describe external or extracellular influences and in the case of claims 144 and 145 the LPS induced expression of cytokines. These influences are, of course, natural phenomena, but the '516 patent claims methods to curtail the effects of these phenomena through human intervention. Dr. Tom Maniatis, one of the inventors of the '516 patent testified as such:

> Q. So, now, how does the patent address the issue of cytokines? What does it tell us about cytokines?
>
> A. Well, the patent basically provides methods to control cytokine production.
>
> Q. Now, how does the patent address the issue of controlling cytokine production?
>
> A. It -- through the manipulation of the NF-kappaB activity.
>
> Trial Tr., Day 3, 62:13-19.

Lilly argues that the purported mechanism of an autoregulatory loop present in cells always reduces NF-κB activity through the production of the NF-κB activity inhibitor protein IκB, which is necessarily activated whenever NF-κB is induced. However, during prosecution the patent examiner was made aware of the concept of negative feedback and allowed the claims of the '516 patent as drawn to various methods for modulating expression of NF-κB-dependent gene expression in mammalian cells using an *agent* which has an effect on the structure or function of NF-κB and/or IκB. Thus, the examiner realized that the claims require an agent administered by human hands to effect the inhibition of NF-κB activity. The specification of the '516 patent also makes clear that the claims are drawn to the artificial manipulation of NF-κB activity that has been induced by an extracellular signal: "[t]he subject invention further relates to methods of regulating (inducing or preventing) activation of NF-κB, controlling expression of the immunoglobulin kappa light chain gene and of other genes whose expression is controlled by NF-κB (e.g. HIV)[1]." ('516 patent col. 3 ll. 54-58).

The claims thus intuitively require human intervention to accomplish a reduction of NF-κB activity *below* the level which may be effected by the natural activity of the IκB inhibitor protein. This obvious reading of the claims is supported by the testimony of the '516 inventor Dr. Phil Sharp - testimony cited by Lilly - which points out the limitations of the IκB activity in the negative feedback process:

> Q. The additional I-kappaB that is produced will bind to NF-kappaB and prevent it from moving to the nucleus; isn't that correct?

[1] "HIV" refers to human immunodeficiency virus, the virus that causes AIDS.

A. Yes, but, again, you have to, you have to say that that's specific to the conditions, because if you're in a state, for example, sepsis, that doesn't happen, because you can't produce enough I-kappaB to shut down the system. It gets -- you know, the receptors on the cell surface are firing *so fast that as the I-kappaB is made, it gets knocked out*.

So it's -- there's not an easy answer to this question, it is a feedback mechanism, but the efficacy of that feedback mechanism depends on the disease state.

Trial Tr., Day 3, 90:1-12 (emphasis added).

This evidence provides context for the claims consistent with their plain meaning as construed by the Court[2] which requires manipulation of NF-κB activity that has been induced by an extracellular signal such that the NF-κB activity will be reduced beyond whatever limited mitigation of NF-κB occurs naturally. Because any natural inhibition of NF-κB through a negative feedback mechanism is limited and especially so under disease conditions like sepsis infections, the '516 patent's method of providing a higher level of NF-κB reduction that will actually modify the effects of external influences is what gives the claims their utility. This is plainly evident from claims 144 and 145 which call for the reduction of LPS induced expression of cytokines - the deleterious proteins triggered by sepsis infections. Thus the asserted claims recite useful and patentable subject matter under § 101.

[2] As construed by the Court reducing NF-κB activity means "decreasing the function of NF-kB to act as an intracellular messenger that regulates transcription of particular genes, **in response to certain stimuli**." (emphasis added).

Much of Lilly's argument on § 101 confuses the issue of patentability under that section with the requirements of novelty under § 102. It appears that Lilly is attempting to push another anticipation argument through the back door of § 101. However, Lilly's evidence that the autoregulatory loop it describes actually existed in nature in a way that accomplished the method of the asserted claims is entirely speculative and surely is inappropriate grounds for resolution under Fed.R.Civ.P. 50(a). A genuine issue of fact exists as to whether the '516 claims as improperly construed by Lilly would encompass natural phenomena. For example, evidence adduced during the case demonstrates that when NF-κB activity is induced by an extracellular influence, the stimulus will cause a net *increase* in NF-κB activity. In other words, an extracellular influence increases NF-κB activity in the cell despite the theorized presence of negative feedback. Nor has Lilly demonstrated that the natural processes to which it alludes reduce the effects of NF-κB activity such as the level of expression of genes. *See,* Claim 95.

Lilly failed to adduce any evidence at trial which could conclusively establish how negative feedback associated with NF-κB activity functions and whether it could meet all of the elements of the asserted claims. While Plaintiffs contend Lilly will not be able to show clearly and convincingly that an autoregulatory loop is invalidating to the claims-in-suit on any ground, Plaintiffs submit that this issue might be better addressed at a hearing at which both parties may offer evidence. This issue was not fully aired at trial in accordance with the Court's decision to decide the issue instead of the jury. Therefore, Lilly's motion under § 101 may not be ripe for adjudication. Should the Court decide that it is, then for the foregoing reasons, Lilly's motion for judgment as a matter of law should be denied and the asserted claims held valid.

Dated May 1, 2006

Respectfully Submitted

By:
/s/ Vladimir V. Drozdoff

Leora Ben-Ami
Patricia A. Carson
Vladimir Drozdoff
KAYE SCHOLER LLP
425 Park Avenue
New York, NY 10022
Tel: (212) 836-8000
Fax: (212) 836-8689

Attorneys for Plaintiffs ARIAD Pharmaceuticals, Inc., Massachusetts Institute of Technology, the Whitehead Institute for Biomedical Research, and the President and Fellows of Harvard College

Lee Carl Bromberg, BBO# 058480
Kerry L. Timbers, BBO# 552293
BROMBERG & SUNSTEIN LLP
125 Summer Street
Boston, MA 02110-1618
Tel.: (617) 443-9292

CERTIFICATE OF SERVICE

I hereby certify that this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non-registered participants on May 1, 2006.